

REMARKS

Interview Summaries:

Applicants thank Examiner Krishnan for the benefit of an interview on October 3, 2006 with the undersigned and Scott Servilla and the follow-up interview on October 11, 2006, during which the scope of the prior art, including Robinson (U.S. Pat. Pub. 2003/0100752) and Niedballa (U.S. Pat. No. 5,275,801), vis à vis the pending claims was discussed.

Applicants respectfully submit this amendment in view of the interviews and in response to the April 14, 2006 Office Action. Upon entry of this amendment, claims 2-5, 8-31, and 34-37 will be pending in the application. Claims 2, 5, 11, 19, 21, 22, 23, 26, 29, 30, and 34 have been amended. Support for the amendments can be found throughout the application; for claims 23 and 29 support is found, *inter alia*, in ¶¶14-15, 36-42. Claims 11, 19, 21, 26, 29, and 30 were amended to further clarify the claims, to correct antecedent basis, and/or to correct grammar. No new matter is included in these amendments.

Reconsideration of the above-referenced patent application in view of the amended claims and following remarks is respectfully requested.

Aspects of the present invention include compounds of tin mesoporphyrin that are ***water soluble***, and methods of making the same. The compounds of the present invention comprise a tin mesoporphyrin complexed with at least one amino acid. The compounds formed in accordance with the present application were analyzed in various ways, including UV/VIS spectra, to confirm that indeed a new chemical species was formed (*see* paragraph 58 of the published application; paragraph 60 of the as-filed application). Paragraph 58 of the published application further explains that, among the reaction products of the various amino acids, “differences ranging from subtle to obvious were observed” for the UV/VIS spectra. An example of an obvious change occurred with amino acids having an aromatic moiety, where the UV/VIS spectra suggested “the likely formation of chemical bonds between the [aromatic-containing] amino acid and the tin mesoporphyrin” (paragraph 55 of the published application; paragraph 57 of the as-filed application). A subtle change in the UV/VIS spectrum occurred for the reaction product

derived from arginine sodium (paragraph 58 of the published application). The term “a tin mesoporphyrin complexed with at least one amino acid” as used herein refers to the chemical species resulting from reacting an amino acid with tin mesoporphyrin, regardless of the extent to which the UV/VIS spectra changes.

Claim Objections

Claims 2 and 23 have been objected to for informalities. Claim 2 has been amended, and the misspelling has been removed. Claim 23 has been amended to fix grammatical errors. Accordingly, Applicants respectfully request that these objections be withdrawn.

Claim 21 has been objected to for allegedly failing to further limit claim 11. Although Applicants respectfully disagree, both claim 11 and claim 21 have been amended to recite an aspect of the invention more clearly. The preamble of claim 11 now is directed simply to a “method.” Claim 21 now depends from claim 19 which depends from claim 11. Claim 19 has been amended to further define the type of tin mesoporphyrin as comprising a tin mesoporphyrin halide. Claim 21 recites further process claims for obtaining the tin mesoporphyrin halide. Accordingly, Applicants respectfully request that this objection be withdrawn.

Claim Rejections – 35 U.S.C. § 112

Claims 1-5 and 8-31 have been rejected under 35 U.S.C. § 112, ¶1 for allegedly failing to comply with the written description requirement due to the addition of the limitation “wherein the tin mesoporphyrin is not derivatized with a complexing agent.” Applicants note that this limitation was only added to claims 2, 5, and 34, and therefore, this rejection has been understood to be directed to claims 2-5, 8-10, and 34-37. Moreover, this limitation has been removed from claims 2, 5, and 34, and Applicants request withdrawal of this rejection as moot.

Claims 1-5 and 8-31 have been rejected as being allegedly indefinite under 35 U.S.C. § 112, ¶2. With regard to the term “complexing agent,” Applicants note that this limitation was added to claims 2, 5, and 34, and not to claim 1. This rejection, therefore,

has been understood to be directed to claims 2-5, 8-10, and 34-37. Because this term has been deleted from these claims, Applicants request withdrawal of this rejection as moot.

As to claim 23, the term “elevated” has been deleted from the claim. Claim 23 has been amended to recite “heating a reaction mixture of a hemin and a hydrogenation catalyst to a first temperature and for a first period of time.” The use of the term “heating...to a first temperature” means that the first temperature is greater than the starting temperature of the hemin and the hydrogenation catalyst. The mixture is held at the first temperature of the first period of time. Accordingly, Applicants request reconsideration and withdrawal of the 35 U.S.C. § 112, ¶2 rejection of claim 23 and the claims depending therefrom.

As to claim 26 and the use of “hydrogen pressure,” claim 23 now provides antecedent basis for this term by reciting a step of supplying hydrogen in the reaction mixture. Accordingly, Applicants request reconsideration and withdrawal of the 35 U.S.C. § 112, ¶2 rejection of claim 26 and the claims depending therefrom.

Claim Rejections – 35 U.S.C. § 102

Claims 22, 29, and 30 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 4,692,440 (Kappas). Kappas is directed to “therapeutic use of tin mesoporphyrin.” Kappas, however, fails to teach or suggest a water soluble complex of a metal mesoporphyrin and at least one amino acid. Claims 22 and 29 have been amended to more clearly recite that the claimed pharmaceutical formulation includes the water soluble complex of the tin or metal mesoporphyrin with the at least one amino acid formed by the methods of claims 11 and 23, respectively. Because Kappas fails to teach or suggest every claim limitation of claims 22, 29, and 30, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 102(b) rejection of these claims.

Claim Rejections – 35 U.S.C. § 103 over Robinson in combination with Drummond and Bettelheim

Claims 2-5, 8-10, 22, 29-31, and 34-37 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Pat. Pub. No. 2003/0100752 (Robinson) in

combination with Annals of New York Academy of Sciences, 1987, 514, 87-95 (Drummond) and General, Organic and Biochemistry, 1998, page 596 (Bettelheim). Applicants respectfully traverse this rejection because the cited art fails to teach or suggest all of the claim limitations, and the office action fails to provide either a proper motivation to combine or an expectation of success.

Applicants note that claim 31 has been included in this rejection, however, claim 23 from it depends, was not rejected in view of any prior art. Clarification is requested.

Robinson Fails to Teach or Suggest the Claimed Invention

Robinson Does Not Teach or Suggest Water Soluble Compounds

Robinson is directed to a broad genus of porphyrin and azaporphyrin derivatives, including compounds having substitution groups of R₁ to R₁₂, variations for which number in the tens of thousands (pp. 45-46). The compounds provided by Robinson are intended to be used “in photodynamic therapy, MRI diagnosis, and radiodiagnostics” (par. 1). By way of background, Robinson discusses that “[c]ompounds with high water solubility are often not taken up efficiently by tumors or cells. The ability to enhance the lipophilicity of the molecule is thus very important” (par. 18). The compounds of Robinson are photosensitive so that they are useful in photodynamic therapy (par. 21).

Claims 2, 5, and 34, recite “a tin mesoporphyrin complexed with at least one amino acid, wherein the compound is **water soluble**.” (emphasis added) Robinson, to the contrary, does not teach a water soluble compound. The office action refers to paragraph 211 of Robinson as teaching “a method of treating psoriasis using the water-soluble mesoporphyrin compounds complexed with amino acid.” But, Applicants respectfully disagree with this characterization.

One skilled in the art, reading paragraph 211 in conjunction with paragraphs 208-210, understands that the compounds of Robinson are **not** water soluble. In order to make solutions in water of the active compounds of Robinson, a surfactant is needed (par. 208). Also, in order to make the compounds of Robinson suitable for injections in a carrier such as water, proper fluidity is achieved by, among other things, creating proper particles sizes and using surfactants (par. 209). The description in paragraph 211 that

compounds can be applied directly to tumors by using water as a solvent, thus, is **not** a teaching that the compounds are water soluble. The water merely suspends the compounds so that the compounds can be delivered to a tumor. Robinson had previously taught the importance of using lipophilic compounds in order to ensure uptake by a tumor (par. 18). Paragraph 211, therefore, cannot support a reading that the compounds of Robinson are water soluble, which are the exact opposite of lipophilic compounds. Robinson, therefore, fails to teach the claim limitation of claims 2, 5, and 34, that the compound is water soluble.

Drummond and Bettelheim Fail to Teach Water Soluble Tin Mesoporphyrin Compounds

Neither Drummond nor Bettelheim, alone or in combination with Robinson overcomes the lack of teaching of water solubility in Robinson. Drummond and Bettelheim are silent on this point. Accordingly, *prima facie* obviousness has not been established because all of the claim elements have not been identified in the cited art.

Robinson Does not Teach Or Suggest Tin Mesoporphyrin Complexed With Amino Acids

In addition, Applicants respectfully submit that that the office action overlooks the guidance offered in MPEP § 2144.08 for analyzing obviousness of a species in light of prior art reciting a genus. MPEP § 2144.08 states:

The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) (Federal Circuit has "decline[d] to extract from *Merck [& Co. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989)] the rule that... regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it."). See also *In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995).

The office action improperly singles out the selection of Applicants' species of tin mesoporphyrin complexed with amino acid from the tens of thousands of species covered by the genus of Robinson. As discussed above, singling out a tin compound and an R group containing an amino acid from Robinson still does not result in a water soluble

compound. For this reason, too, the office action fails to establish *prima facie* obviousness.

MPEP § 2144.08 provides a decision tree, including consideration of the size of the genus disclosed, whether there are express teachings that would have motivated the selection, where there is a teaching of structural similarity, and whether there are any other teachings to support the selection. As to this analysis and as discussed above, the genus disclosed by Robinson is so broad that it cannot inherently disclose the selection of a metal mesoporphyrin complexed with an amino acid resulting in a water soluble compound. Further, Robinson does not provide express teachings to arrive at the selection nor does Robinson teach of structural similarity. In fact, rather than providing express teachings to arrive at a tin mesoporphyrin compound as recited in Applicants' claims, Robinson teaches otherwise. Paragraph 163 of the published patent application states: "Particularly advantageous are the porphyrins based on chloroporphyrin e6 (9), chloroporphyrin e4 (10), phylloporphyrin (11), rhodoporphyrin (7), pyrroporphyrin (8), pheoporphyrin a5 (13) and phylloerythrin (12) and compounds having similar ring systems." Paragraph 166 of Robinson expresses a second preferred class of compounds as being mono-, di-, tri- and tetra azoporphyrins. These statements fail to point to Applicants' claimed compounds. The office action fails to meet the requirement stated in MPEP § 2144.08 that "Office personnel should point out the express disclosure which would have motivated one of ordinary skill in the art to select the claimed invention."

No Motivation to Combine Robinson with Drummond and Bettelheim

In addition, the office action fails to provide a proper motivation to combine the cited references. To begin, the office action cites to Robinson paragraph 211, which discloses the use of its compounds dispersed in cream or salve formulations for *topical* applications, which may be useful for psoriasis (emphasis added). The office action then points to Drummond, which discloses the use of Sn-protoporphyrin *in vivo* to treat heme metabolism. One skilled in the art reading Robinson would not have been motivated to combine its teachings with Drummond. Since the individual references deal with different problems (manufacture of agents for photodynamic therapy that are lipophilic versus use of solutions to treat heme metabolism), there is no commonality in the subject

matter. Robinson seeks to provide lipophilic (not water soluble) compounds that are photosensitive (par. 18, 21). And, incidentally, the compounds can be used to treat psoriasis according to paragraph 211. Drummond addresses a different medical condition using compounds that are not intended to be photosensitive.

Further, the combination of Bettelheim with either Robinson or Drummond is unsupported as well. Neither Robinson nor Drummond identifies the problem of water insolubility of metal mesoporphyrin compounds, and thus, one skilled in the art would not have been motivated to rely on the disclosure of Bettelheim. The office action states that since Bettelheim teaches that amino acids exist as zwitterions and are polar, this renders them soluble in water. This “teaching” is combined with the teaching of Robinson to arrive at the conclusion that one of ordinary skill in the art would recognize that complexing the tin mesoporphyrin of Robinson with amino acids would render them water soluble. However, as noted above, Robinson teaches that the compounds should be lipophilic, not water soluble. The office action, therefore, fails to set forth *prima facie* obviousness because there is no motivation to combine the cited art.

Further, the office action is silent as to any expectation of success that one skilled in the art may achieve by combining Robinson, Drummond, and Bettelheim. For this additional reason, the office action fails to set forth *prima facie* obviousness.

As to other teachings to support the selection, Applicants submit that the office action has failed to meet its burden. As previously discussed, there is no motivation to combine Robinson with Drummond and/or Bettelheim.

In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 103 rejection over Robinson in view of Drummond and Bettelheim.

Claim Rejections – 35 U.S.C. § 103 over Niedballa

Claims 11-20 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 5,275,801 (Niedballa). Applicants respectfully traverse this rejection.

Niedballa is directed to porphyrin complex compounds. Niedballa teaches deuteroporphyrin and hematoporphyrin derivatives that contain a complexing agent K to which a metal can be attached (Col. 13, line 59 to Col. 14, line 2). Any acidic groups of deuteroporphyrin and hematoporphyrin derivatives can be neutralized with basic amino acids (Co. 14, lines 3-12). Niedballa, however, fails to teach or suggest the step of forming a water soluble complex of tin mesoporphyrin and at least one amino acid, as recited by claim 11. Because *prima facie* obviousness has not been established, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 103 rejection of claims 11-20.

Moreover, Applicants respectfully point out that neither the office action nor Niedballa provides *any* teaching or suggestion of claim 15 regarding the ratio of the tin mesoporphyrin to amino acid being at least about 2:1 or of claim 16 regarding the ratio of the tin mesoporphyrin to basic solution being at least about 1:3. For this additional reason, *prima facie* obviousness has not been established in particular for claims 15 and 16 and, therefore, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 103 rejection of claims 15-16.

CONCLUSION

In view of the foregoing remarks, the application is believed to be in condition for allowance, and early notice to this effect is earnestly solicited. If allowance of this application may be expedited by resolution of simple issues through a telephone conference, the Examiner is welcome to call the undersigned.

Applicant has attached a Petition for a three-month Extension of Time and authorization to charge the appropriate fee therefor. If any other fees in connection with this requested Amendment are due however, the Examiner is authorized to charge Deposit Account No. 50-3329.

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Respectfully submitted,

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